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Leber's "plus": neurological abnormalities in patients with Leber's hereditary optic neuropathy

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Abstract

Previous studies suggest that Leber's hereditary optic neuropathy (LHON) may be a systemic disorder with manifestations in organs other than the optic nerves. To evaluate nervous system involvement 38 men and eight women with LHON were re-examined. The patients were divided into three groups according to mtDNA analysis—namely, patients with the 11778 or with the 3460 mutation and patients without these primary mutations. Fifty nine per cent of patients had neurological abnormalities but there was no significant difference between the three groups. Movement disorders were the most common finding; nine patients had constant postural tremor, one chronic motor tic disorder, and one parkinsonism with dystonia. Four patients had peripheral neuropathy with no other evident cause. Two patients had a multiple sclerosis-like syndrome; in both patients MRI showed changes in the periventricular white matter. Thoracic kyphosis occurred in seven patients, five of whom had the 3460 mutation. In one patient the 3460 mutation was associated with involvement of the brain stem. It is suggested that various movement disorders, multiple sclerosis-like illness, and deformities of the vertebral column may associate pathogenetically with LHON.

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Leber's hereditary optic neuropathy (LHON) is an optic nerve disease that causes blindness and is associated with maternally inherited mitochondrial DNA (mtDNA) mutations. Half of the families with LHON have a point mutation at the nucleotide 11778 in the subunit 4 and 15% at the nucleotide position 3460 in the subunit 1 of complex 1.[1 2] Several other mutations have also been postulated to be pathogenic to LHON.[3–5] There are clinically confirmed LHON families with yet undiscovered mtDNA mutation(s).

The disease is characterised by acute or subacute bilateral visual loss usually in young men. The acute stage of the disease is recognised by typical fundus findings, peripapillary microangiopathy, and a swollen retinal nerve fibre layer. Peripapillary microangiopathy fades from view when optic atrophy develops. The fundus findings in the acute stage can be minimal and easily overlooked. Some authors consider that acute LHON can exist without any signs of peripapillary microangiopathy.[6]

Clinical studies suggest that LHON is a system disorder associated occasionally with neurological, cardiac, and skeletal changes.[6 7] Newman, in a recent review, used the term Leber's "plus" to describe patients with the clinical features of LHON in addition to other severe neurological or systemic abnormalities. Multiple sclerosis-like illness, spinal cord disease, brain stem and basal ganglia involvement, and Charcot-Marie-Tooth disease, as well as skeletal changes have been considered to be such abnormalities.[8–17] The purpose of this study was to assess the frequency and type of neurological dysfunctions occurring in Finnish patients with LHON.

Patients and methods

Forty six patients with LHON (38 men, eight women) from 24 families with the disease were neurologically re-examined. The ophthalmological abnormalities in relation to various mtDNA mutations are reported elsewhere.[18] The patients were divided into three groups according to mtDNA analysis, performed as reported previously.[1] There were 27 patients with the 11778 mutation and nine with the 3460 mutation. The third ("other") group comprised 10 patients without these primary mutations. This group had five patients who did not harbour any of the primary mutations; however, two brothers had the 12811 and the 13967 mutations in the ND5 subunit and two brothers the 4732 and the 13637 mutation in the subunits ND2 and ND5 respectively, and in one patient no complex I mutation was detected. All the patients with unknown mutation had a typical acute stage of LHON. The patients received a full neurological assessment supplemented with a review of their previous medical records. Ancillary neuroradiological examinations were performed on nine patients.

Results

Twenty seven patients (59%) had neurological abnormalities in addition to LHON; 15 had the 11778 mutation, six had the 3460 mutation, and six were from the third group. The single most common abnormality was a postural and action tremor of the hands

Neurological and skeletal abnormalities

	11778 (n = 27)	*3460 (n = 9)*	*Other (n = 10)*	*Total (n = 46)*
Migraine	1	3	—	4
Epilepsy	1	1	1	3
Dementia	1	—	—	1
Polyneuropathy	8	—	1	9
Tremor	5	4	5	14
Parkinsonism and dystonia	—	1	—	1
Chronic motor tic	1	—	—	1
Multiple sclerosis-like disorder	1	—	1	2
Brain stem involvement	—	1	—	1
Thoracic kyphosis	2	5	—	7
Pes cavus	—	1	—	1

(table). It occurred in 14 patients belonging to all three mutation groups. In five patients the tremor occurred occasionally in situations known to exaggerate physiological tremor, such as muscle fatigue, anxiety, or after excessive alcohol intake. Nine patients had constant hand tremor with an amplitude not larger than 5 mm for several years; in two cases there was an additional head tremor. Five of these patients had a family history of a similar tremor. Four patients had several maternal relatives with tremor and one male patient had a daughter with a similar tremor.

Altogether nine patients had clinical evidence of a peripheral neuropathy. All these patients except one had the 11778 mutation. The patients had sensory complaints in the feet with decreased or absent ankle jerk and diminished light touch and vibration sense. In two more severely affected patients, nerve conduction velocities were only slightly decreased suggesting a predominantly axonal neuropathy. In five patients, alcohol was possibly the cause or a contributing factor to neuropathy whereas in the remaining four patients no evident cause was found. Migraine occurred in four patients; none had aura. Seizures were experienced by three patients. In two of them, the convulsions had occurred during alcohol withdrawal, and one had complex partial seizures of temporal lobe origin. One woman with the 11778 mutation developed bilateral optic neuropathy at the age of 59. The course of her LHON has been described in detail elsewhere.[19] When examined two years later because of gait difficulty, she was profoundly demented and had a moderately severe peripheral neuropathy. A heavy use of alcohol remained as the most probable cause of her neurological ailment. One male patient had chronic motor tic disorder.

Skeletal abnormalities were noted in seven patients. In all cases kyphosis or kyphoscoliosis occurred in the thoracic region. In two patients with the 11778 mutation, the deformity was only of moderate degree whereas in the other five patients with the 3460 mutation (two from one family and three from another) the kyphosis was pronounced. The case histories of four patients are described in detail.

PATIENT 1

Patient 1 has an extrapyramidal syndrome and carries the 3460 mutation. His LHON was diagnosed in 1985 when he was 29 years old. He developed parkinsonism at the age of 34. The first symptoms were dragging and tremor of the left leg. Tremor soon appeared in the left hand. When examined two years after the onset, he was hypomimic, had a rather severe rest tremor in his left leg and hand with nuchal and left sided rigidity. Brain CT and MRI were normal. He was treated with combined levodopa, bromocriptine, and selegiline with a beneficial response initially. One year later he developed serious nuchal dyskinesia with the head turning to the left and backwards and closely resembling cervical dystonia. All medications were gradually withdrawn with no improvement of the dyskinesia. Even after a 12 month drug free period the patient had cervical dystonia in conjunction with left sided rest tremor and rigidity. Levodopa treatment was reinstituted with relief of rigidity and tremor but no change in dystonic head movements. Injections of botulinum toxin A into cervical muscles initially relieved the dystonia but the efficacy was lost after two treatments. A repeated MRI of the brain was normal.

PATIENT 2

Patient 2 is a woman with the 11778 mutation. She was born in 1938 and has a multiple sclerosis-like illness. At the age of 24 she developed temporary double vision. Two years later she experienced acute left optic neuropathy associated with hyperaemia and disc swelling. The visual acuity in this eye deteriorated during three weeks to permanent finger counting vision. Three years later the right eye was similarly involved. During the acute stage there was hyperaemia and swelling in the disc and definite peripapillary microangiopathy. This eye also became blind during the subsequent weeks. Simultaneously she developed difficulties with her balance. Her legs became stiff and her gait was impaired. Neurological examination showed a spastic paraparesis. She was diagnosed as having multiple sclerosis. When aged 49, she was reevaluated. The visual acuity in her right eye was finger counting at 1 m and in the left eye, hand movements. She had no near vision. The pupils reacted slightly sluggishly to light. Biomicroscopy was normal and intraocular pressure 13 bilaterally. Both visual fields had a large, absolute centrocecal scotoma. Ophthalmoscopy showed severe disc pallor and retinal nerve fibre loss. She has been examined neurologically several times and her condition has steadily deteriorated. Treatment with intravenous methylprednisolone has been of no objective benefit. At the last neurological examination she was confined to a wheelchair. There was a mild weakness in the right arm together with an intention tremor with a final amplitude of some millimetres. Her legs were weak and spastic. Both arm and leg reflexes were increased with extensor plantar responses. Vibration sense was diminished up to the iliac crest. She had urgency of micturition and occasional incontinence. Her CSF contained 3 lymphocytes/mm^3; there were oligoclonal

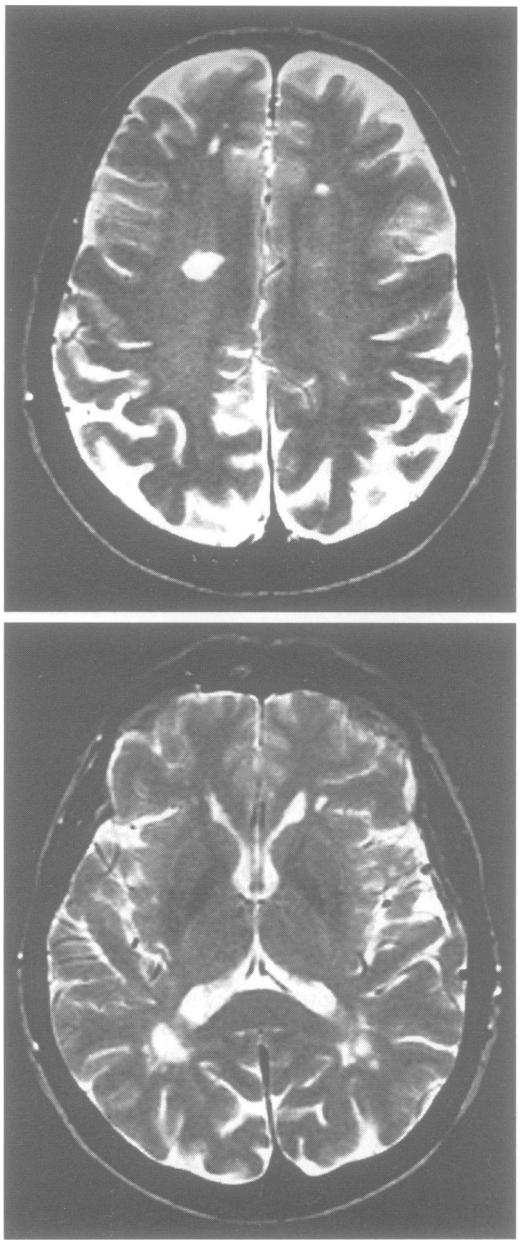

Figure 1 T2 weighted brain MRI showing white matter changes and small putaminal necrotic areas.

bands and increased IgG content. Brain MRI disclosed white matter and putaminal lesions with increased T2 signal (fig 1).

PATIENT 3

Patient 3 is a man with the 12811 and the 13967 mutations at ND 5. He was born in 1937 and has a multiple sclerosis-like illness. At the age of 18 his left eye was affected and three months later his right eye was also involved. According to his medical chart both fundi showed neurovascular changes in the acute stage suggestive of LHON. During subsequent years he noticed increasing weakness and stiffness in his legs. In neurological examination he was found to have a mild spastic paraparesis. An air myelogram was normal. His CSF was otherwise normal, but a gold colloidal curve was interpreted as slightly abnormal. Paraparesis steadily worsened and at the age of 50 years he was confined to a wheelchair. Ten years later the visual acuities were finger counting at 1–2 metres. He had no near vision. Pupils were 7 mm with normal light reactions. Ophthalmoscopy showed severe disc pallor and retinal nerve fibre loss bilaterally. When examined neurologically at the age of 55 he was able to walk only a few metres with support. Cranial nerve functions except optic nerve involvement were normal. The reflexes were increased in his arms and there was bilateral slight intention tremor. His legs were weak and spastic; reflexes were increased with ankle clonus and bilateral extensor plantar responses. There was a sensory deficit for light touch and vibration up to the 10th thoracic dermatome. He had urinary incontinence and failure to achieve erection. Brain MRI showed periventricular small lesions with increased T2 signal; additionally, there were widened sulci in the temporal region bilaterally. Cervical MRI disclosed a spinal stenosis at the level of the 5th to 7th cervical vertebrae. A cervical laminectomy at C5 to C7 was performed without any relief of paraplegia. His brother also developed typical LHON with peripapillary microangiopathy progressing to permanent blindness. The brother has postural tremor but a neurological examination was otherwise uninformative. There are no other affected family members.

PATIENT 4

Patient 4 is a man with the 3460 mutation. He was born in 1946 and has eye movement disturbance and kyphosis. At the age of 32 years he experienced an acute LHON which deteriorated rapidly to severe permanent blindness. In 1994 the visual acuity in the right eye was perception of light and in the left eye, hand movements only. The pupils reacted somewhat sluggishly to light. Biomicroscopy and intraocular pressures were uninformative. The optic discs were totally pale and the peripapillary arterioles narrow. There was no visible nerve fibre layer. His visual fields could not be assessed because of severe blindness. The left eye was exotropic. The adduction was restricted bilaterally, more in the left eye. He could not converge his eyes. The vertical eye movements were also restricted, more upwards than downwards. There was no optokinetic response. He had increased reflexes, but the plantar responses were flexor. The vibration sense was absent at the ankles. There was no ataxia. He had pes cavus and pronounced kyphosis in the thoracic spine (fig 2). Brain MRI disclosed a slight pontine and cerebellar atrophy, additionally there were widened sulci in the frontal and occipital cortices. No changes in white matter were seen.

Discussion

Leber[20] described minor neurological symptoms and signs in his patients with LHON. Other authors have reported headaches, emotional instability, reflex abnormalities, polyneuropathy, seizures, mental retardation, and other non-specific neurological signs in their patients.[21 22] In the present study four patients with migraine and one patient with

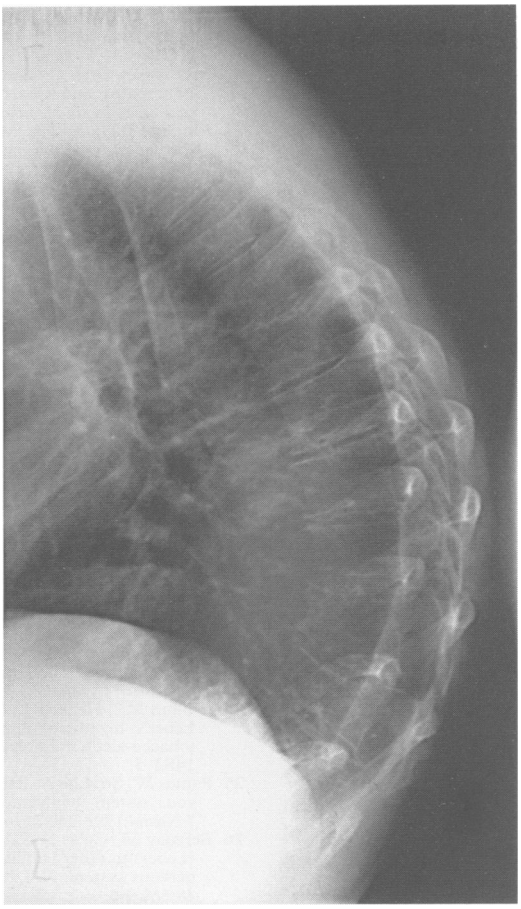

Figure 2 Radiograph of thoracic spine showing a thoracic kyphosis. The vertebrae show anterior body and plate irregularity, disc space narrowing, and small Schmorl's nodes (Scheuermann changes).

epilepsy belong to this category. The combination of alcoholism and LHON was relatively common as also reported by others.[23 24]

Tremor in association with LHON has been reported by several authors.[11 17 26-29] In our families tremor was seen in all three subgroups. The clinical nature of the constant tremor in nine patients was identical to the features of essential tremor. Essential tremor is known to be inherited dominantly in an autosome; the location of the gene, however, is not known. The pathogenesis of essential tremor is unknown and no pathological changes have been found in the brain.[30] In a population based epidemiological study the prevalence of essential tremor was 5·5% in a Finnish population aged over 40.[31] Tremor occurred in 20% (nine of 46) of our patients with LHON, four of them having maternal relatives with similar tremor. This may suggest a more specific connection of tremor with LHON. We have not studied the paternal offspring and thus cannot exclude the possibility of simultaneous autosomally inherited essential tremor in these families.

One of our patients with the 3460 mutation had parkinsonism and cervical dystonia. A similar case has been reported by Larsson *et al.*[11] They described a patient with the 11778 mutation who developed unilateral tremor and rigidity one year after optic nerve involvement at the age of 36. Brain MRI showed sharply defined lesions bilaterally in the putamina. This type of striatal putaminal necrosis with prominent dystonic symptoms coseggregating with LHON pedigrees has been reported by several authors.[8 15 21 29 32-35] Interestingly, Jun *et al* recently showed that the family with LHON and dystonia originally reported by Novotny *et al*[15] had a mtDNA mutation at nucleotide pair 14459 of the NADH dehydrogenase subunit 6 gene.[36] The disorder usually but not necessarily appears during childhood.[8 15 32] It is noteworthy that patients in Leber's "plus" families may develop only the movement disorder, which suggests that the phenotypes of Leber's "plus" families may vary.

Early medical literature and more recent papers[9 12 16 37-39] have suggested that a multiple sclerosis-like illness may accompany LHON. Harding *et al*[9] showed widespread white matter lesions in five neurologically affected female patients and in two female patients with LHON only. All these patients had the 11778 mutation. The authors suggested that this type of neurological disorder occurs only in women and that mitochondrial genes may contribute to the susceptibility to multiple sclerosis. We found multiple sclerosis-like illness in one female and one male patient. These patients with progressing spastic paraparesis closely resemble the cases described in the medical literature; both of them also showing scattered white matter lesions. The female patient carried the 11778 mutation, and the male patient had the 12811 and the 13967 mutation of ND5 indicating that multiple sclerosis like disorder is not restricted to women or to the 11778 mutation.

In the present study the association of neuropathy with LHON still remains only suggestive. Johns *et al* reported that the 15257 mutation has a high incidence of spinal cord and peripheral neurological symptoms.[10] In the present study we had seven patients from a family with the 15257 mutation. Two of these patients had mild polyneuropathy but in other patients the neurological examination was uninformative. All these patients simultaneously harboured the 11778 mutation and thus the relevance of the 15257 mutation in the pathogenesis of LHON cannot be evaluated.

Two patients with a multiple sclerosis-like syndrome reported by Harding *et al* had internuclear ophthalmoplegia.[9] Paulus *et al* recently described a patient with the 11778 mutation who developed brain stem involvement with Parinaud's syndrome and oculopalatal myoclonus.[25] In this case MRI showed a high signal area in the brain stem corresponding to a hypodense area on CT. Apparently the brain stem may be involved in LHON, at least subclinically. This hypothesis is supported by Mondelli *et al* who reported anomalous brain stem auditory evoked potentials in seven of their 11 patients with LHON.[40] Our patient with restrictions in eye movement may represent brain stem involvement of LHON.

Vertebral column deformities were common in the present study. Seven patients had thoracic kyphosis, one also with pes cavus. There are previous descriptions of kyphoscoliosis, arachnodactyly, spondyloepiphyseal dysplasia, and short stature associated with

LHON.[26-29 32] Kyphosis has also been noted in the families with LHON that exhibit spastic dystonia syndrome.[29] In the present study the high incidence of kyphosis in two non-related families with the 3460 mutations suggests that it could represent one phenotypic feature of the 3460 mutation. We have, however, not studied the paternal relatives in these families and thus the autosomal inheritance of kyphosis cannot be excluded.

Peripapillary microangiopathy is one of the main findings in LHON. Bruyn *et al* suggest that endothelial swelling of the lenticulostriatal vessels could produce anoxia or ischaemia and explain the symmetric or even strictly unilateral putaminal lesions seen in the spastic dystonia syndrome.[8] Also the white matter lesions detected in multiple sclerosis-like disease could be caused by microangiopathy. Abnormal, enlarged mitochondria with complicated cristae in the pericytes of capillaries, endothelial cells, and smooth muscle cells of the small arteries in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke like episodes (MELAS), one of the mitochondriopathies, has been reported by several authors suggesting that abnormalities in small arteries might be responsible for the stroke like episodes of the disease.[41-43] We suggest that in the enigmatic aetiopathogenesis of LHON progressive microangiopathy may also be an important factor in neurological manifestations, and warrants further exploration.

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